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Epidural dexamethasone showed a better analgesic profile over epidural betamethasone as adjuvant in acute neuropathic lumbar pain

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Keywords*— *epidural dexamethasone, epidural betamethasone, epidural lidocaine, acute neuropathic pain, ocular pressure.

***Abstract*—** *Background: The study was designed to evaluate dexamethasone and betamethasone as adjuvants in epidural management of acute radicular pain related to pain, ocular pressure, weight gain and systemic effects. Methods: Twenty six patients with neuropathic pain secondary to disc herniation acted as their own control related to the epidural administration of dexamethasone and betamethasone. Thirteen patients have started with dexamethasone during the first two weekly procedures, and after 3 weeks of wash-out were submitted to two weekly sequences of sacral betamethasone and cross-over. Patients were evaluated related to analgesia, blood pressure, ocular pressure, weight gain, adverse effects and plasmatic measurements of ions, glycemia, ACTH and cortisol. Results: Dexamethasone was superior to betamethasone analgesia ($p<0.05$). Plasma cortisol and ACTH reduced on the 7th day after the block ($p<0.001$). The plasmatic concentrations of the ions Na^+, K^+, Ca^{++}, control and post-prandial glycemia, blood pressure, weight were similar between groups and did no differ from initial control values ($p>0.05$). Three patients that received dexamethasone after the firs block and 2 that received betamethasone had cortisone glaucoma on day-7 ($p<0.001$). Discussion: Epidural dexamethasone/lidocaine analgesia was superior to betamethasone/lidocaine analgesia and both drugs resulted in similar unaware increase in ocular pressure and sleep disturbance.*

I. INTRODUCTION

Although the indication of epidural corticosteroids as part of the treatment of acute neuropathic pain when the conservative treatment have failed is well recognized,[1,2,3] there have been concerns related to which corticosteroid would be the best indication, as there is the risk of particulate aggregation and serious adverse effects secondary to their own pharmacological properties or intra vessel aggregation and obliteration.[4,5,6] Besides, there is no available information regarding the non-particulate dexamethasone or the

particulate betamethasone would offer better efficacy for analgesia effect. The study was aimed to evaluate their analgesic and systemic effects.

II. METHODS

This clinical protocol and patient consent forms were designed in accordance with the revised Declaration of Helsinki and the Good Clinical Practice of the International Conference on Harmonization and approved by the Ethics Committee of the School of Medicine of Ribeirão Preto, University of São Paulo (USP) (Reg 14302010). Blood analysis was done at the Laboratry Center of Pharmacometry and Toxic Analysis, School of Pharmaceutical Sciences of the U.N.E.S.P., Araraquara. The prospective study was conducted at the Clinic for Pain Treatment- EPPA- Comprehensive Level, at the same hospital. Each patient acted as his/her own control after writing informed consent.

This prospective study comprised 26 consecutive patients at the Pain Center with clinical history of neuropathic lumbar pain (less than 3 months) secondary to disc herniation at L4-L5 or L5-S1, which diagnostic was based on clinical and magnetic resonance, who accept participating, who previously underwent conservative treatment with physical therapy under oral medication, albeit complaining of pain classified as VAS > 3 cm (VAS 0-10 cm).[7] The concept of visual analog scale (VAS), which consisted of a 10 cm line with 0 equaling "no pain at all" and 10 equaling "the worst possible pain" was introduced.

During this period, all patients were taking daily combination of 25 mg amitriptyline before bedtime, dipyrone three to four times daily and diclofenac 50 mg three times daily during the first 5 days. After introduction into the study, it was maintained only amitriptyline 25 mg and diclofenac was kept as rescue analgesic as part of the protocol. Subjects had to be willing and able (e.g. mental and physical condition) to participate in all aspects of the study, including use of medications, completion of evaluations, attending the scheduled clinic visit and compliance with protocol requirements as evidenced by providing written, informed consent. Patients were excluded from the study for the following reasons: evidence of clinically unstable disease, renal problems, glaucoma or history of glaucoma in the family, psychiatric disease, refusal or known allergy to the devices used, diabetes, previous cardiac infarction or angina, coagulation disturbance, or infection.

Patients acted as their own control related to the epidural administration of dexamethasone and betamethasone. Thirteen patients started with dexamethasone during the first two weekly procedures (Dexa group (G)), and after 3 weeks of wash-out were submitted to two weekly sequence of sacral betamethasone (Beta G). The other patients have started with epidural betamethasone, followed by dexamethasone after 3-week rest. Patients were evaluated related to analgesia, blood pressure, ocular pressure, weight gain, adverse effects and plasmatic measurements of ions, glycaemia, ACTH and cortisol. Demographics characteristics were noted regarding all patients.

The caudal block was performed with either 10 mg dexamethasone or 10 mg betamethasone combined to 40 mg lidocaine diluted to final 10 ml volume with normal saline. The blocks were performed in the operating room with the aid of the fluoroscopy and non-iodinated contrast. Motorization for all patients consisted of non-invasive blood pressure, pulse oximetry and continuous electrocardiography. Patients were maintained on light sedation with 2 mg IV midazolam combined to 100 mcg IV alfentanil, administered in order to keep conscious sedation.

Blood pressure, ocular pressure (with Perkins tonometer, measured by the same ophthalmologist), weight (kg), pulse rate, plasmatic measurements of glycaemia, Na^+, K^+ and Ca^{++} were evaluated before each block during all the study period. Glycosylated hemoglobin was evaluated on days 1 and 35 (just before 1st and 3rd block, respectively, Figure 1). Plasmatic cortisol and adrenocorticotrophic hormone (ACTH) were evaluated on days 1, 7 and 35 for both drugs (Figure 1). However, only all 13 patients scheduled for the participation in the first part of the study were included for each drug evaluation related to cortisol and ACTH, after the administration of either dexamethasone during two consecutive weeks in 13 patients, or after the betamethasone administration in 13 patients.

Analgesia was evaluated by VAS pain scores (0-10 cm), and by number of rescue analgesic consumption. As rescue analgesics, it was prescribed 50 mg diclofenac at 8-hour interval if necessary (VAS > 3cm). Figure 2 describes the VAS measurements prior to first block during the two moments of the study after the 3-week wash-out period. For the VAS, all patients were included in the final evaluation for both drugs. The rescue analgesic consumption was equally evaluated in two times (days 14 and 49 of the study) including all patients. The VAS at day-7 reflected analgesia after the first block, while the VAS at day-14 reflected the analgesia after the 2nd block. Similarly, the VAS at day-42 reflected the analgesia after the third block (second moment of the study after wash-out period), and VAS at day-49 reflected the analgesia after

the 4th block (Figure 1). Rescue analgesic consumption was evaluated as mean daily tablet numbers at day-14 and at day 49 for both groups.

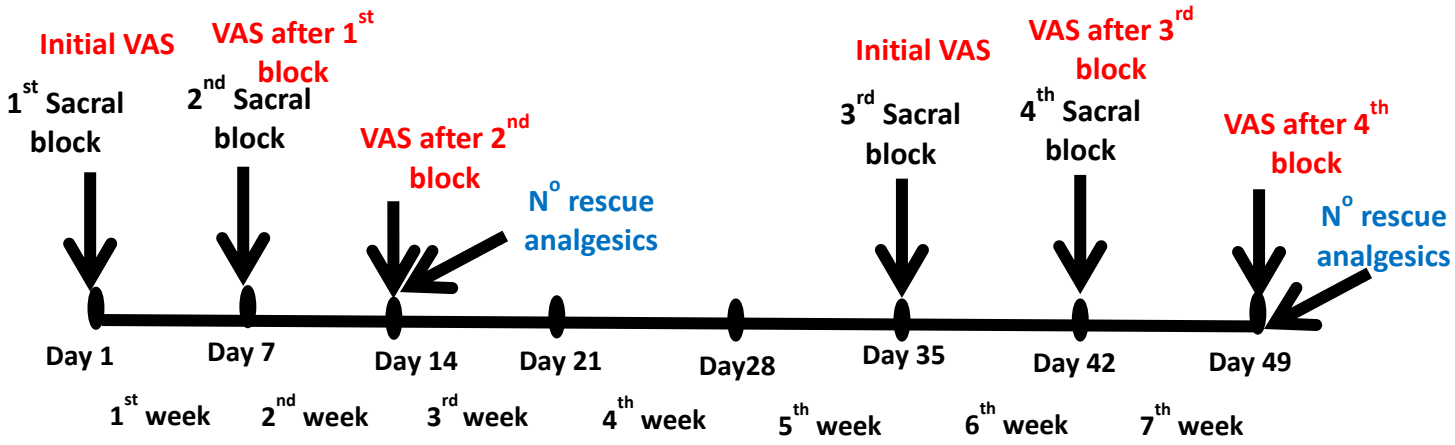

Fig.1. Study organograma for pain evaluation

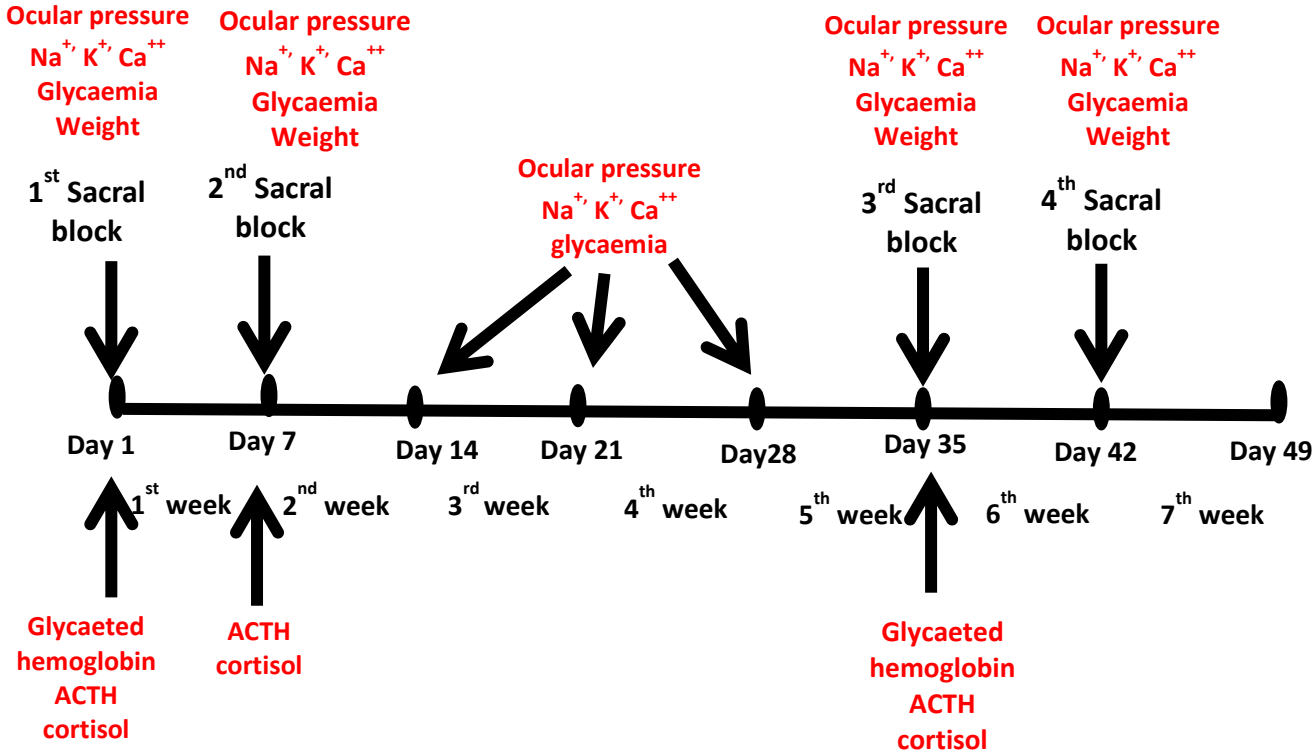

Fig.2. Organogram of the study related to blood collection and ocular pressure.

III. STATISTICS

The power of the study was based upon preliminary data. We hypothesised that the dexamethasone analgesia would be 40% improved compared to epidural betamethasone. With a beta value of 80% and an alpha value of 0.05, these assumptions would require at least 18 patients. P<0.05 was considered significant. Data are expressed as mean±STD, unless otherwise stated. The study included 26 patients to avoid bias..

The normality of the data was evaluated by the Shapiro Wilkings test. Demographic data was described. The statistical analysis was performed using Friedman and Wilcoxon signed-rank test. Significance was set at $P<0.05$. Adverse effects were described.

IV. RESULTS

The final data set included 23 subjects. One patient from Dexa G was excluded from the study due to

loss of blood material. The second patient excluded (from Beta G) did not come to receive the fourth block. Finally, a third patient from Dexa G refused to continue the study due to intense vaginal pruritus after the first block.

Thirteen patients were female and ten male. The mean time for pain prior to the study was 3±1 weeks. The variability of weight (kg) was similar when compared the weight before each block, at days 1, 7, 35 and 42 ($p>0.05$); independent of the phase of the study. The pain VAS prior to the study was 8±2 cm for the 23 patients. However, on day 7, patients from Dexa G showed lesser pain scores compared to the Beta G at both day-7 and day-14 (Day 7- 3±1 cm; *versus* 5±1 cm; $p<0.05$) (Day 14- 2±1 cm; *versus* 3±2 cm; $p<0.05$) (Figure 3). After 3 weeks wash-out, prior to start the second phase of the study protocol, the patient who have been previously during the first phase to the Dexa G showed lesser VAS scores showed lower scores compared to the first phase of Beta G during the day-35 ($p<0.05$). However, Figure 4 refers to the second phase of the study, and by the 42th and 49th days of the study, both groups were similar ($p>0.05$). Related to the number of rescue analgesics at day-14 and at day-49 for both groups, the Dexa G had a lower diclofenac rescue analgesic consumption 1(0-1) tablets (25% a 75%) and 2(2-3) (Beta G) at day 35 ($p<0.05$), however similar for both groups on 42th and 49th days.

Mean blood pressure was similar during all weeks of the study for all patients ($p>0.05$, data not shown). Related to ocular pressure, 5 of 23 patients (22%) had cortisone glaucoma on day-7. The mean ocular pressure of those 5 patients prior to the study was 13±2 mmHg (similar to the others of the study group $p>0.05$). However, on the 7th day evaluation, the mean ocular pressure of the 5 patients was 30±3 mmHg ($p<0.001$). These patients were followed by a Glaucoma specialist, and all used beta-blocker eye drops to keep ocular pressure between 10-15 mmHg. However, one of the patients underwent trabeculectomy surgery.

The plasmatic concentration of Na^+ (mean 140±3 mEq/l), K^+ (mean 4±0,3mEq/l) Ca^{++} (mean 9,7±0,4mEq/l) fasting blood glucose (92±6 mg/dl), blood glucose 120 minutes after food ingestion (mean 114±7 mg/dl), and glycated hemoglobin (mean 5.2±0.3%) were similar during all study week evaluations ($p>0.05$).

The cortisol plasmatic concentrations (µg/dl) were lower at day-7 compared to day-1 ($p<0.001$), but similar to day-35 ($p>0.05$) for both groups. Table 1 describes the plasmatic cortisol levels at 1st, 7th and 35th days for the Dexa G and Beta G. Table 2 describes the ACTH plasmatic levels (pg/dl) at 1st, 7th and 35th days ($p<0.01$) for the groups. Similarly, the ACTH plasmatic concentrations were lower at day-7 compared to day-1 ($p<0.01$), but similar to day-35 for both groups ($p>0.05$).

Table 1. Plasmatic cortisol (µg/dl) for Dexa G and Beta G at days 1st, 7th and 35th.

	Dexa G	**Beta G**
Day 1	21.5±5.65	21.7±5.79
Day 7	11.5±4.07	11.2±3.32
Day 35	25.3±2.14	26.5±5.68
P	1st day >7th day 35th day > 7th day 1st day = 35th day	1st day >7th day 35th day > 7th day 1st day = 35th day

Mean ± STD. Dexa G- dexamethasone group; Beta G- betamethasone group

1st day > 7th day 1st day ($p<0.001$), but similar to 35th ($p>0.05$) for both groups

Table 2. Plasmatic ACTH (pg/dl) for Dexa G and Beta G at days 1st, 7th and 35th. day-7 It was lower at the 7th day compared to the 1st day ($p<0.01$), but similar to 35th day ($p>0.05$).

	Dexa G	**Beta G**
Day 1	27.5±5.68	26.9±7,27
Day 7	15.3±2.86	15.8±4,39
Day 35	25.9±2.14	24.1±2.91
P	1st day >7th day 35th day > 7th day 1st day = 35th day	1st day >7th day 35th day > 7th day 1st day = 35th day

Mean ± STD. Dexa G- dexamethasone group; Beta G- betamethasone group

1st day > 7th day 1st day ($p<0.001$), but similar to 35th ($p>0.05$) for both groups

Related to adverse effects, one patient from Dexa G refereed intense vaginal pruritus and felt discomfortable, refusing to continue the study protocol. Another two patients from Beta G felt epigastralgia. Although 16 of 23 patients referred difficulty to sleep from the 1st -3rd day after sacral block, they did not take it as adverse effect, as they felt disposition during the following days. No others complain were noted.

V. DISCUSSION

The results revealed that epidural 10 mg dexamethasone was clinically superior to epidural betamethasone related to analgesia, with similar adverse effects. The Dexa G showed less pain VAS scores during the study evaluation at day-7, day 14 , day-42 and day 49

($p<0.05$). In addition, the Dexa G also showed lesser number of rescue analgesic consumption at day 14 and day-49 ($p<0.05$). Moreover, there was no change in weight and blood pressure during all study evaluation and no differences regarding the plasmatic concentration of Na^+, K^+, Ca^{++}, fasting blood glucose, blood glucose 120 minutes after food ingestion, and glycated hemoglobin during the study evaluation ($p>0.05$).

Recently, a systematic review of 26 total studies revealed that epidural steroids decreased the need for surgery as a primary outcome examined the same patient cohort.[8] In addition, we have decided for lidocaine, as an effect of crystallization has been described for the combination of ropivacaine and the non-particulate steroid dexamethasone.[9] Besides, 7 other meta-analysis studies demonstrated superior analgesic effect of lidocaine combined to steroids.[10] Apart from blocking presynaptic expression of functional Tetrodotoxin-Resistent Na^+ channels and shaping presynaptic action potentials and transmitter release at the first sensory synapse,[11] spinal lidocaine may be involved preventing noxious stimuli by attenuating Nav1.3 up-regulation and suppressing activation of spinal microglia.[12] as well as inhibiting persistent Na^+ current in the damaged dorsal ganglion.[13] Its effective anti-inflammatory action on neuropathic pain may also be secondary to lidocaine promotion of the suppressors of cytokine-signaling protein 3 expression in microglia, in turn suppressing $IBA1^+$ microglia accumulation and p38 MAPK and NF-κB.[14]

Corticosteroids been used frequently in pain treatments since 1952. Due to a review of the complications as a result of their application in epidural injections, the United States of America Food and Drug Administration issued an "alert controversy" requesting that a warning label should be added to injectable corticosteroids, where risks must be described, such as loss of sight, brain damage, paralysis and death) when administering by this route.[15] Even the time of preparation superior to 5 minutes may induce aggregation of betamethasone.[17] Nevertheless, epidural steroids are still a good option via the sacral route,[16] and dexamethasone was the nonparticulate steroid of choice.[16] Related to steroids, epidural dexamethasone had an attenuating effect on the peripheral inflammatory tissue injury induced hyperalgesia and this effect was mediated through the inhibition of intraspinal cytosolic phospholipase A_2 expression and the primary site of action was the laminae I-II of the spinal cord.[18] Moreover, dexamethasone treatment significantly reduced the levels of immune mediators, and prevented inflammatory and/or neurodegenerative lesions in the central and peripheral nervous systems, and apoptosis in the dorsal root ganglia.[19] There is also a suggestion that dexamethasone could resolve brain inflammation possibly through microglial phenotypic switching from pro-inflammatory M1 to anti-inflammatory M2.[20]

Concerning the plasmatic evaluation, both the control levels of cortisol and ACTH were similar between groups prior to the study (Tables 1 and 2), but reduced at day-7 ($p<0.01$). However, at day-35, cortisol and ACTH levels returned to baseline in both groups ($p>0.05$), in accordance to others.[21] The ions Na^+, K^+, Ca^{++}, fasting plasma and post feeding plasma glucose were similar among groups when evaluated before each block for both groups($p>0.05$). In accordance to others,[22] fasting glucose plasma levels was back to baseline values on the third day after the epidural administration of steroid, and after 2[23] to 4[24] days in diabetic patients. That would explain why our values were all back to baseline on day-7.

When the ocular pressure was evaluated, 3 patients from Dexa G and 2 from Beta G had an increase of ocular pressure on day-7 in the order of 30 mmHg, while normal ocular pressure is taken between 8 to 20 mmHg.[25] Cortisone glaucoma is directly linked to a corticosteroid treatment.[26] Among the risk factors it is described diabetes, myopia, young age; and the mode of steroid administration.[25,27] Increase in ocular pressure to 30 mmHg is taken clinically as cortisonic glaucoma, and is described from 7 to 30 days after systemic steroids, with an incidence of 12.8%.[27] A different study suggested that patients over 51year-old were more susceptible to increase ocular pressure after intravitreal dexamethasone.[28] Clinically, 4 of the patients had good response to eye drops, but one of them was submitted to trabeculectony three months after the episode.

Apart from ocular pressure, other adverse effects were described although not statistically significant, albeit the power of the study was based on analgesia effect. One of the patients referred intense vaginal pruritus and was excluded from the study.[29] Its mechanism of action is not well known, its incidence is not significant, however its discomfort was considered catastrophic by the patient. Although 16 of 23 patients referred insomnia after the caudal steroid administration for up to three days, it was not taken as a problem by the patients, as they felt disposition during the day-time. That would justify the low incidence described by others.[30]

As conclusions, caudal dexamethasone combined to lidocaine resulted in superior analgesia compared to caudal betamethasone and lidocaine, and both drugs resulted in unaware increase in ocular pressure and sleep disturbance.

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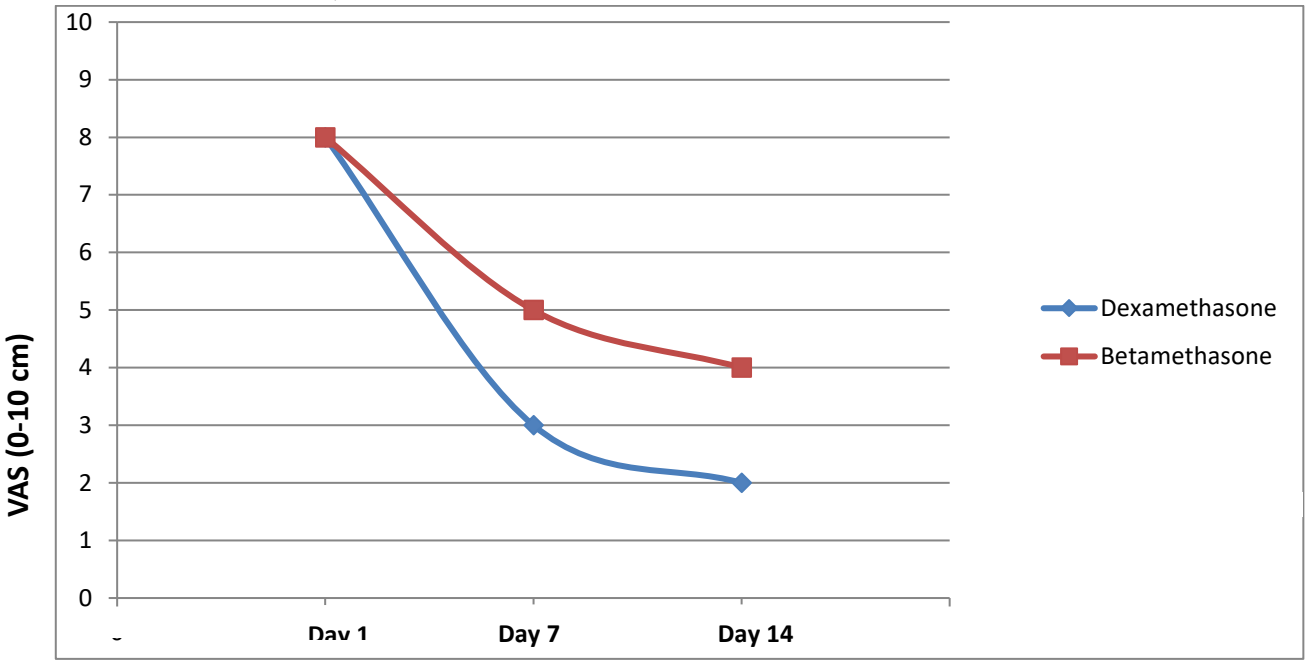

Fig.3. Pain VAS scores (0-10 cm) for groups Dexa G and Beta G just prior of the block. P<0.05 at 1st, 7th and 14th –day Dexamethasone group < Betamethasone group at days 7th and 14th(p<0.05).

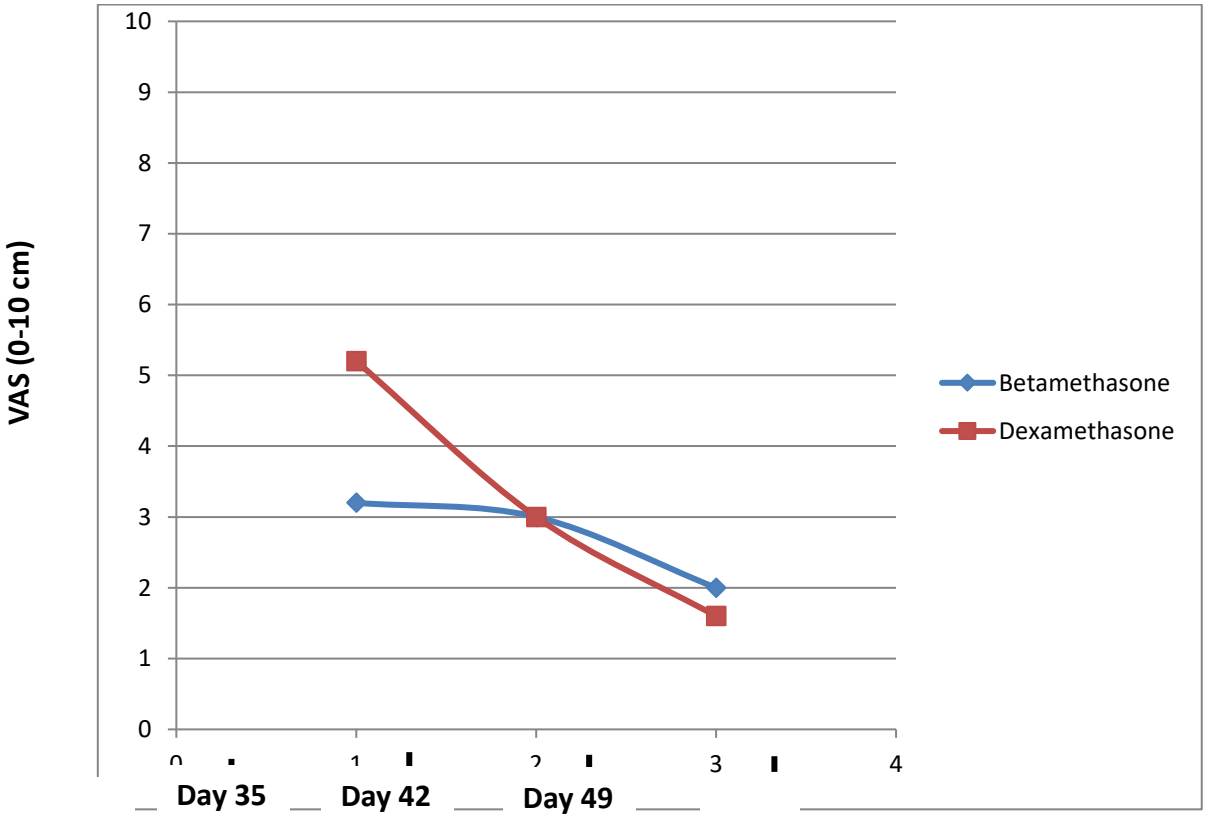

Fig4. After the wah-out, the cross-over of the groups. Pain VAS scores (0-10 cm) for groups DexaG and Beta G. Dexa G < Beta G at 35th day (p<0.05).